IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Gwong-Jen J. Chang
Application No. 10/500,796
Filed: July 6, 2004
Confirmation No. 5091
For: NUCLEIC ACID VACCINES FOR PREVENTION OF FLAVIVIRUS INFECTION

FILED VIA EFS

Examiner: Jeffrey S. Parkin, Ph.D.
Art Unit: 1648
Attorney Reference No. 6395-64909-02

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DECLARATION UNDER 37 C.F.R. § 1.132

1. I, Gwong-Jen J. Chang, Ph.D., am the sole inventor named in the above-referenced patent application. I am the Team Leader of the Molecular Epidemiology & Immunochemistry Lab, Arboviral Diseases Branch, Division of Vector-Borne Infectious Diseases, at the Centers for Disease Control (CDC). I have been employed by the CDC for 20 years and have conducted research in the fields of virology and epidemiology for 27 years. I have published more than 60 peer-reviewed scientific articles in the fields of virology, epidemiology and vaccine development. A copy of my biographical sketch is submitted herewith (Exhibit A).

2. I have read and understood the above-referenced patent application, including the pending claims, and the Office action dated March 26, 2008.

3. It is my understanding that in the March 26, 2008 Office action, claims 1-17, 28, 30, 32, 34, 36 and 44-54 were rejected as allegedly obvious over Yasui *et al.* (*Southeast Asian J. Trop. Med. Public Health 21(4)*:663-669, 1990) in view of Kochel *et al.* (U.S. Patent No. 6,455,509), Ivy *et al.* (U.S. Patent No. 6,136,561), Phillpotts *et al.* (*Arch. Virol. 141*:743-749, 1996) and Kozak (*J. Mol. Biol. 196*:947-950, 1987). It is also my understanding that this rejection was based on the conclusion by the Office that it would have been obvious to one of ordinary skill in the art to prepare a transcriptional unit encoding a Japanese encephalitis virus

(JEV) signal sequence in combination with an antigen from another flavivirus, or with a chimeric flavivirus antigen.

4. The claimed nucleic acid molecules comprising a transcriptional unit encoding (i) a JEV signal sequence and (ii) an immunogenic antigen from another flavivirus or a chimeric flavivirus antigen, exhibit unexpectedly superior results over the cited references, which is evidenced by the data described in the specification and discussed below.

5. The specification (see Example 9 beginning on page 48) describes the pCBWN plasmid (SEQ ID NO: 15), which encodes a JEV signal sequence and the prM/E proteins from West Nile virus. As described in Example 11 (beginning on page 53 of the specification), mice vaccinated with pCBWN produced neutralizing antibodies, and a single inoculation with pCBWN resulted in complete protection from virus challenge. In addition, horses vaccinated with a single dose of pCBWN were completely protected and showed no signs of illness following virus challenge. The vaccinated horses also produced significant levels of neutralizing antibody following vaccination.

6. The specification (see Example 20 beginning on page 65 of the specification) further describes the construction of dengue virus plasmids pCD9D2-1J-4-3 (SEQ ID NO: 44) and pCB8D2-2J-2-9-1 (SEQ ID NO: 46) in which the transcriptional units encode a JEV signal sequence, the prM protein from dengue virus and a chimeric E protein having sequences from both JEV (10% or 20%) and dengue virus (90% or 80%). All mice inoculated with a single dose of pCB8D2-2J-2-9-1 seroconverted within three weeks of immunization and 50% of mice receiving a single inoculation of pCD9D2-1J-4-3 had seroconverted at three weeks. In addition, two sequential inoculations of pCB8D2-2J-2-9-1 resulted in the production of neutralizing antibody in 9 of 9 mice, indicating that vaccination with this construct would be effective against virus challenge. Indeed, attached as Exhibit B is a manuscript that I co-authored (Chang *et al.*, *Virology* 306:170-180, 2003), which describes the effectiveness of the dengue virus constructs. The data provided in the Chang *et al.* manuscript demonstrates that a single dose of pCB8D2-2J-2-9-1 in female mice confers passive protection by maternal antibody to suckling pups. In addition, suckling pups of vaccinated mice survived challenge with a wild-type strain of dengue virus (see page 175 of Chang *et al.*).

7. The data provided in the specification and in Chang *et al.* (Exhibit B) demonstrate that a single dose of a flavivirus DNA vaccine comprising the claimed transcriptional units provides 100% protective immunity from lethal flavivirus challenge, elicits significant neutralizing antibody titer, and provides passive protection by maternal antibody. These results are unexpectedly superior over the results that one of ordinary skill in the art would expect based on the teachings of the prior art, such as the references cited by the Office.

8. None of the references cited by the Office, or in the prior art, teach a JEV signal sequence in combination with an immunogenic antigen from another flavivirus, or a chimeric flavivirus antigen. Although Yasui *et al.* teach the importance of the JEV signal sequence for expression of antigenic JEV proteins, one would not have been able to predict based on this teaching and other teachings in the art that a JEV signal sequence could be used in combination with an antigen from a heterologous flavivirus, or with a chimeric flavivirus antigen, to produce an immunogenic flavivirus antigen, particularly an immunogenic antigen capable of eliciting 100% protection from lethal virus challenge. Kochel *et al.*, Ivy *et al.* and Phillpotts *et al.* do not even teach JEV signal sequences. Thus, the claimed transcriptional units exhibit unexpectedly superior results over the combination of references cited by the Office.

9. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: June 24, 2008

Gwong-Jen J. Chang, Ph.D.